

U.S.S.N. 10/012,202

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copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, vinyl acetate, azo polymers, pectin, chitosan, amylose, guar gum, and zein or combination thereof.

A3 28. (currently amended) The antihistamine composition defined in claim 19 wherein the analgesic agent, antitussive agent, expectorant, anti-inflammatory agent or decongestant is in an immediate release form or in a sustained release form.

29. (original) The antihistamine composition defined in claim 28 wherein the sustained release effect is achieved by formulating the analgesic agent, antitussive agent, expectorant, anti-inflammatory agent or decongestant with a sustained-release control polymer selected from the group consisting of methyl cellulose, ethyl cellulose, wax, gums, cellulose acetate, cellulose acetate phthalate, hydroxypropylmethylcellulose succinate, polyvinyl acetate phthalate, acrylic acid polymers and copolymers, polymers or copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, vinyl acetate and combination thereof.

Remarks**Amendments to the specification**

The paragraph beginning at line 19, page 8, has been amended to incorporate the time range of non-sedating antihistamine release defined by originally filed claim 7. The paragraph beginning at line 28, page 12, has been amended to incorporate the time range of sedating antihistamine release defined by originally filed claim 13.

Amendment to claim 28

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Claim 28 is amended to define the antihistamine composition as in an immediate release form or a sustained release form. Support is found at p. 10, lines 9-15, particularly lines 14 and 15.

Rejection Under 35 U.S.C. § 103

Claims 1-29 were rejected as obvious under 35 U.S.C. §103(b) over U.S. Patent No. 5,451,409 to Rencher et al. ("Rencher"); U.S. Patent No. 5,827,852 to Russell et al. ("Russell") in view of Rencher; or U.S. Patent No. 5,648,358 to Mitra ("Mitra") in view of Rencher. The applicant respectfully traverses the rejections.

The Claimed Invention

The claims define a biphasic antihistamine composition in daily oral uni-dosage or divided dosage form and a method of making and using the composition. The dosage form contains two monophasic parts, each having an active ingredient which is either a sedating antihistamine or a non-sedating antihistamine (p. 7, line 15 to p. 8, line 9). The claimed composition has the advantage of (1) avoiding sedating effects of sedating antihistamine during the day time and (2) taking the full advantage of sedating antihistamine in the night time (p. 9, lines 5-13), while only needing to be administered once a day. The claimed composition achieves this advantage by being formulated so that only non-sedating antihistamine is released in the day, and only sedating antihistamine is released at night (p. 8, line 10 to p. 9, line 4). Various delayed or sustained release formulations and coatings (p. 10, lines 9-25; p. 13, lines 1-13; p. 13, line 18 to p. 28, Examples 1-3) are used to achieve this release profile.

Dependent claims are drawn to compositions comprising specific sedating antihistamines (claims 2, 3, 14 and 15) or a therapeutically effective amount of an

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additional agent (claims 8, 19, 25, 28 and 29). The composition can have a specific release profile of the sedating or non-sedating antihistamine or the additional agent (claims 4-7 and 16-18). The sedating or non-sedating antihistamine can be formulated into a sustained release form or a delayed release form (claims 24-27 and 29) using at least one delayed release control polymer or at least one sustained release control polymer defined therein.

As shown in Examples 1-3, procedures are taken to ensure the biphasic feature of the composition such that the sedating antihistamine is released in the night or evening time but not released in the day time and the non-sedating antihistamine is released in the day time but not released in the night time.

Rencher

Rencher describes a single "homogeneous matrix" containing one or more actives, from which each active component is released at an appropriate rate to provide the desired activity over a period of 2 to 24, preferably 8 to 12 hours (col. 2, lines 21-27). The formulation uses a polymer blend of hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC) to control the release rate of the active components (col. 1, line 60 to col. 2, line 5). It is important to note that the composition, upon administration, provides sustained; *not delayed*, release, releasing the active component at a rate to provide the desired activity over a period of 2 to 24 hours (col. 2, lines 26-27). The active component is released immediately at an effective level and remains such over a period of 2 to 24 hours. This is clearly seen in Tables 6 and 8, which shows that the composition can release 15 to 26 percent of the active component within 30 minutes after administration.

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Therefore, Rencher fails to make obvious the claimed subject matter because Rencher does not:

- (1) teach delayed release nor, more importantly,
- (2) recognize the benefit of a formulation of both a sedating antihistamine and a non-sedating antihistamine, which are released at different time periods.

Rencher is not particularly drawn to the delivery of antihistamines. The use of sedating antihistamine is not of a concern. Therefore, Rencher does not provide the motivation for one of ordinary skill in the art to make and use the claimed composition. Moreover, Rencher teaches making a homogeneous composition of the active ingredients. In contrast, as the foregoing discussion shows, a biphasic composition as defined in any of the claims 1-29 is necessary to achieve the release profile defined in claims of the present application. Therefore, even if one argued that Rencher provided motivation for one of ordinary skill in the art to make and the composition defined in any of claims 1-29, Rencher would not lead one of ordinary skill in the art to have a reasonable expectation of success of the claimed composition and method of using the composition. As such claims 1-29 are not *prima facie* obvious over Rencher under 35 U.S.C. 103 (*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141). Further, in emphasizing a homogeneous composition, Rencher teaches away from the claimed biphasic composition.

Russell

Russell describes a pharmaceutical composition suitable for coating a drug for treating cold, cough, allergy, and flu symptoms (col. 2, lines 42-67). The active

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ingredient can be an antihistamine (col. 5, lines 37-42). The composition can be formed of triturate active ingredients which were "blended together" (col. 7, line 45 to col. 8, line 67, particularly col. 8, lines 33-35, Examples I-III). The active ingredients in a composition of a blend of triturate active ingredients do not distinguish one from another in terms of the timing and the rate of release. Therefore, the composition described in Russell, without more, would not delay the release of any of the active ingredients. It certainly cannot prevent the release of one of the active ingredient in the day time.

Russell teaches forming a simple blend of triturate active ingredients while Rencher teaches forming a homogenous composition. Therefore, Russell in combination with Rencher, fails to teach one skilled in the art to (1) make a biphasic composition; (2) for delivery of a sedating antihistamine during the night and a non-sedating antihistamine during the day time.

Accordingly, Russell in view of Rencher would not render claims 1-29 *prima facie* obvious under 35 U.S.C. 103 (*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141).

Mitra

Mitra describes a composition for the treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms (col. 2, lines 19-24). The composition contains caffeine and pyrrolidine and piperidine ethers (col. 2, lines 24-45). The pyrrolidine and piperidine ethers have antihistamine properties (col. 2, lines 46-47). The composition is formed of triturate active ingredients or liquid formulation of the ingredients with other fillers or excipients (col. 5, line 15 to col. 6, line 67, Examples 1-V). One of ordinary skill in the art knows, a composition formed of a blend of triturate

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active ingredients cannot avoid release of any of the active ingredients at any point in time, much less a defined period such as the day time.

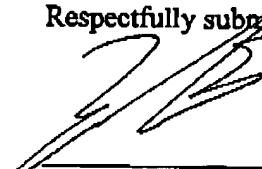
Therefore, Mitra in combination with Rencher fails to teach or make obvious a biphasic composition for delivery of a sedating antihistamine in the night and a non-sedating antihistamine in the day time. Mitra teaches forming the composition described therein by blending triturate active ingredients while Rencher teaches forming a homogenous composition defined therein, therefore teaching away from the claimed composition. Accordingly, Mitra in view of Rencher would not render claims 1-29 *prima facie* obvious under 35 U.S.C. 103 (*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141). Further, Mitra, which teaches forming a composition by blending triturate active ingredients, and Rencher, which teaches forming a homogeneous composition of the active components defined therein, teach away from the claimed composition which is biphasic.

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Allowance of all claims 1-29 are earnestly solicited.

Respectfully submitted,



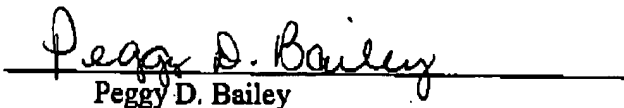
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Response to Office Action and all documents shown as being attached is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Date: May 15, 2003



Peggy D. Bailey

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